

Study Title: Bariatric Embolization of Arteries for the Treatment of Obesity (BEAT Obesity)

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**ORIGINAL APPLICATION FOR
INVESTIGATIONAL DEVICE EXEMPTION (IDE)**

Feasibility and Safety Study:

Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss

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1 INTRODUCTION

1.1 Study Title

Feasibility and Safety Study: Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss

1.2 Sponsor

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1.3 Background / Clinical Rationale

1.3.1 Stomach is an Endocrine Organ

Although there are over 40 hormones that limit food intake, there is only one hormone, ghrelin that has been shown to be orexigenic, i.e., to stimulate food intake. Discovered by Kojima et. al. in the rat stomach, it was shown to induce growth hormone release by acting on the growth hormone secretagogue receptor (GHS-R) in the hypothalamus or anterior pituitary(1). Since the identification of this neuropeptide, extensive data in both animals and humans have shown its potent orexigenic effects(2). Mechanisms to antagonize or suppress the effects of ghrelin on the central nervous system have resulted in dramatic weight loss and change in appetite in various studies(2, 3). In studies performed on volunteers, intravenous ghrelin stimulates meal initiation, with nearly half of all volunteers describing a sensation of hunger with a compensatory increase of 28% in caloric intake(4) . Further evaluation has shown that, in humans, there is a consistent pattern associated with ghrelin levels, which rise shortly before, and fall immediately after, every meal. In situations such as weight loss, there is a compensatory increase in ghrelin levels which may contribute to the difficulty in maintaining body weight(5). In obese patients, foods fail to suppress systemic ghrelin levels, which could impair postprandial satiety and may initiate overeating. Due to the potent orexigenic effect of ghrelin, this hormone has been a target for the treatment of obesity and weight loss. Although various reports of ghrelin suppression have been described, none are clinically practical

1.3.2 Anatomy of the Gastric Fundus

The stomach is classically separated into seven major sections: cardia; fundus; antrum; pylorus; lesser curvature; greater curvature; and the angularis (**Figure 1A**). While each section of the stomach has a unique role in the digestive process, the fundus serves as the epicenter for the neuroregulatory pathway of the stomach involved with satiety and appetite stimulation (6-9). Since ghrelin is expressed mainly in the fundus, it contains 10 to 20 times more ghrelin per gram of tissue than the duodenum, the next richest source, and has a higher GHS receptor activation than the hypothalamus(10, 11) . Notably, the vascular supply to the gastric fundus is distinct, identifiable, and can be accessed with a catheter from a percutaneous approach. The dominant flow to the fundus arises from the left gastric artery, which is the first branch off the celiac axis (**Figure 1B**).

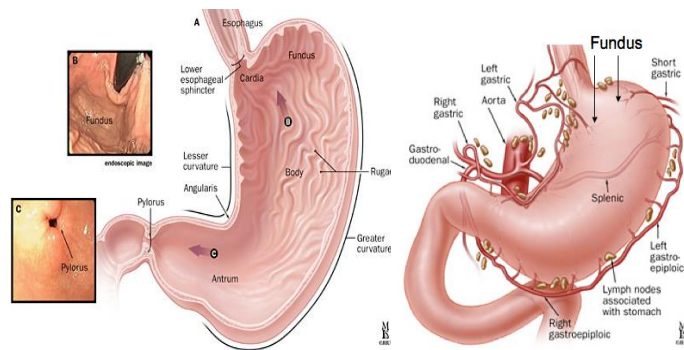


Figure 1A: Anatomic drawing of the different sections of the stomach. Figure 1B: Vascular supply to the stomach.

In fact, transcatheter gastric arterial embolization has been performed for at least three decades and has been shown to be effective at controlling acute gastrointestinal hemorrhage. Embolization works by effectively interrupting blood flow. In addition, the GI tract has a rich, collateral blood supply, with extensive vascular arcades that allow for safe embolization without ischemia. Thus, bariatric arterial embolization (BAE) is already a clinically viable procedure and is currently the standard of care in patients whose condition is refractory to endoscopic control of gastrointestinal bleeding.

1.3.3 Ghrelin Suppressed after Gastric Bypass Surgery

More recently, ghrelin appears to have a significant role in the long-term effect of weight loss in bariatric surgery. Since bariatric surgery isolates the gastric fundus from ingested nutrients, ghrelin profiles are shown to be lower by 77% compared to controls(6, 12-14). Furthermore, the normal diurnal pattern is interrupted and the meal-initiated fluctuations are blunted(6, 12). Based on all these findings, achieving low systemic ghrelin levels should become a strategy to control obesity and maintain weight loss.

1.4 Study Synopsis

This is an Investigator-sponsored clinical investigation. The purpose of this IDE study is to evaluate the safety and feasibility of bariatric embolization as a new minimally-invasive image-guided therapy for morbid obesity in which specific blood vessels to the stomach are blocked in order to suppress the body's signals for feeling hungry, leading to weight loss.

In this submission, we propose the investigational use of a legally-marketed device for a new intended use: the clinical use of calibrated microspheres for bariatric embolization. Thus, this study would be considered physiologic research of the impact of bariatric embolization on the systemic hormonal levels of obesity and its impact on weight gain.

This study will recruit 20 patients in a prospective single arm study to evaluate the feasibility, safety and toxicity of bariatric embolization. This study will be performed jointly at two institutions.

The guiding hypothesis of this study is to prospectively test, that transvascular bariatric embolization results in safe and effective weight loss in morbidly obese patients. The duration of the study (time to enrollment of last patient + follow-up period) will be approximately two years.

2 DEVICE DESCRIPTION

2.1 Introduction

The legally marketed Embosphere Microspheres (Merit Medical., Jordan, Utah) will be used to perform the bariatric embolization procedures.

2.2 Design

Embosphere Microspheres are part of a family of embolic materials based on Merit Medical's proprietary microsphere technology. These spheres are designed to offer controlled, targeted embolization.

Embosphere Microspheres are biocompatible, hydrophilic, nonresorbable, microspheres produced from an acrylic polymer and impregnated with porcine gelatin. Embosphere Microspheres are available in a range of calibrated sphere sizes..

The embolization particles are available in six sizes: of 40-120 um, 100-300 um, 300-500 um, 500-700 um, 700-900 um, and 900-1200 um, to enable appropriate size selection for the tumor or malformation to be treated. Embosphere Microspheres are designed for use under fluoroscopic guidance through compatible delivery catheters. The product is provided as a sterile, non-pyrogenic, single use device.

Additional Embosphere product information can be found at the Merit website :<http://www.merit.com/products/default.aspx?code=embosphere>

2.3 Regulatory Status

Device Product Codes: 85 NAJ

Classification Name: Artificial Embolization Device

Regulation Numbers: 21 CFR 882.5950

Trade Name: Embosphere Microspheres

510(k) Number: K021397

Indications for Use: Embosphere® Microspheres are indicated for the embolization of hypervascular tumors, arteriovenous malformations and uterine fibroids.

2.4 Anticipated Modifications to the Device and Instrumentation

There are no anticipated changes to the device during the course of this clinical investigation.

3 REPORT OF PRIOR STUDIES

3.1 Pre-Clinical Studies

These pre-clinical studies were not performed under GLP. All animal studies were performed in a University setting where GLP facilities were not available.

3.1.1 Bariatric Embolization with Sclerosing Agent

In the initial studies by our group, a direct link between the gastric arteries and systemic levels of ghrelin has been demonstrated.(15, 16) Using a chemical sclerosing agent, sodium morrhuate, to selectively ablate the gastric fundus from a transarterial approach, ghrelin suppression was achieved, probably in part due to the deep penetration of liquid embolic agents. In our initial studies, Bariatric arterial embolization (BAE) was performed in five swine by the selective infusion of sodium morrhuate (125 mcg), a chemical sclerosing agent, into the gastric arteries that supply the fundus(15, 16). Five controls underwent a sham saline procedure.

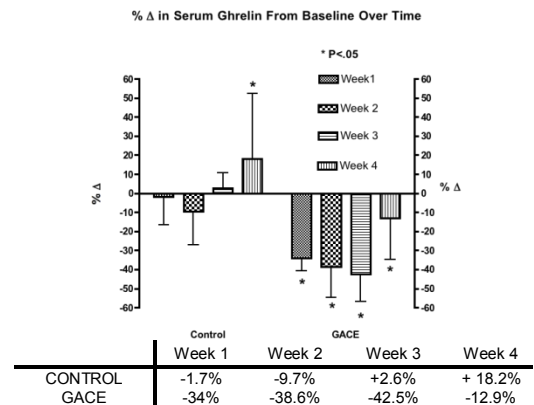
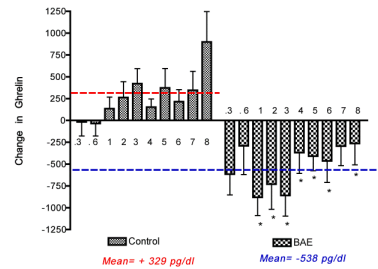
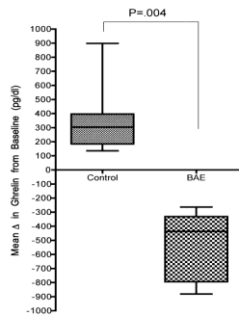


Fig 2: Percentage change from baseline in serum ghrelin in control and BAE swine embolized with sodium morrhuate (mean±SEM) over a four-week period. In control swine, there was no change in systemic ghrelin from baseline until week 4. In BAE swine, ghrelin decreased at all timepoints with maximum

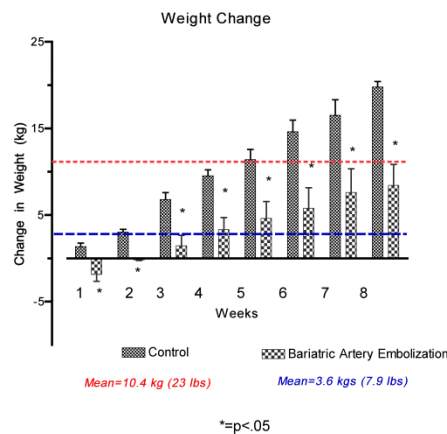
The pattern of the change in ghrelin levels over time was significantly different between control and treated animals ($p < 0.004$, Fig 2). In treated animals, ghrelin levels were significantly reduced at weeks 1-4 relative to baseline (range 12.9-42.5% decrease). Control swine continued to gain weight (a 15.1% increase from their original weight), whereas BAE-treated swine weights only increased 7.8%. Importantly, non-target embolization (NTE) was seen frequently in hepatic, splenic, and esophageal arteries in almost all animals. Since these agents are very toxic, extensive tissue necrosis occurred and, thus, this agent is not a clinically viable option.

3.1.2 Bariatric Embolization with Calibrated Spheres

We next tested whether commercially available calibrated microspheres could cause long-term suppression of systemic ghrelin levels and affect weight gain. In twelve healthy growing swine, BAE was performed by the selective infusion of 40µm-calibrated microspheres (Celonova Biosciences, San Antonio, Texas) into the gastric arteries that supply the fundus ($n=6$), while six control pigs received a sham saline injection. All animals underwent endoscopy at three weeks to assess for ulceration or stricture. As anticipated, the average weekly change in ghrelin levels was reduced between BAE-treated and control animals and reached statistical significance at weeks 1-6 and week 8 (Fig 3), with average post-procedure ghrelin values significantly reduced from baseline for treated animals compared to control animals ($-537.9 \text{ pg/dl} \pm 209.6$ vs. $328.9 \text{ pg/dl} \pm 129.0$, $P = 0.004$). In addition, the average change in weight was significantly reduced between BAE-treated and control animals and reached statistical significance at week 1 and weeks 3-8 (Fig 4). Despite the fact that microsphere BAE significantly decreased weight in treated pigs, ulcers were visualized on endoscopy and histopathology in treatment animals, i.e., 33% of animals at three weeks. Furthermore, almost all ulceration appeared in the stomach antrum, rather than in the gastric fundus.



*Fig 3: (Left) Mean change in ghrelin (over eight weeks) in control animals vs. swine that underwent BAE. (Right) Average weekly change in ghrelin in control and in animals that underwent BAE. Ghrelin levels were significantly reduced in treatment animals at weeks 1-6 and week 8. * $p < 0.05$*



*Fig 4: % Change in weight in treated and control swine. Weekly mean weight change from baseline was significantly different between treatment and control animals at weeks 1 and weeks 3-8. * $p < 0.05$*

Tissue animals and bariatric in Figures 5 eight weeks, detection of antighrelin

MAB10404, Millipore, Billerica, MA) was determined as the number of positive cells/400X high power field. Ghrelin-immunoreactive cell density was significantly lower in the gastric fundus in the treated animals vs. controls (15.3 vs. 22, $p = 0.001$, Fig 5). Yet, ghrelin-immunoreactive cell density in the duodenum was similar in treated and control animals (8.5 vs. 8.6, $p = \text{NS}$).

3.1.3 Bariatric Embolization with Calibrated Spheres -Histology

sections in control treatment animals after embolization are shown and 6. After sacrifice at immunohistochemical ghrelin (mouse IgG in a ratio of 1:4000,

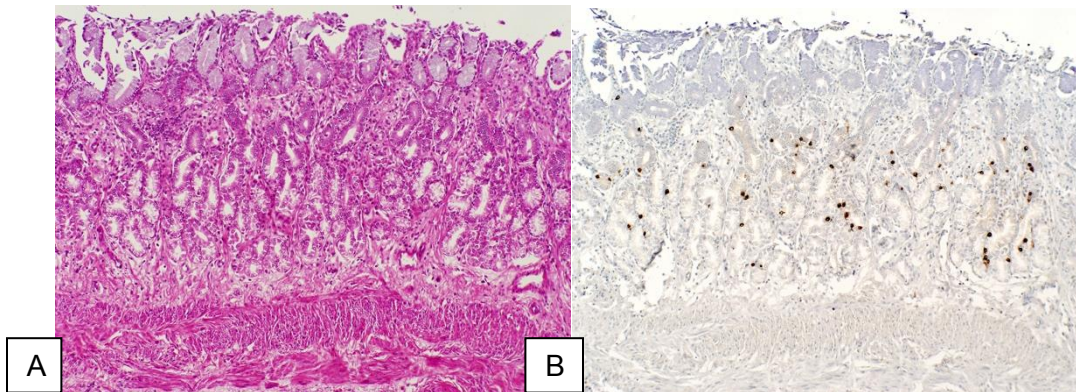


Figure 5. A, Section of gastric fundus from control animal showing preservation of the mucosa with no evidence of ischemic damage (H&E, x100). B, Immunohistochemical staining for ghrelin from the same area shows several ghrelin expressing cells (x100).

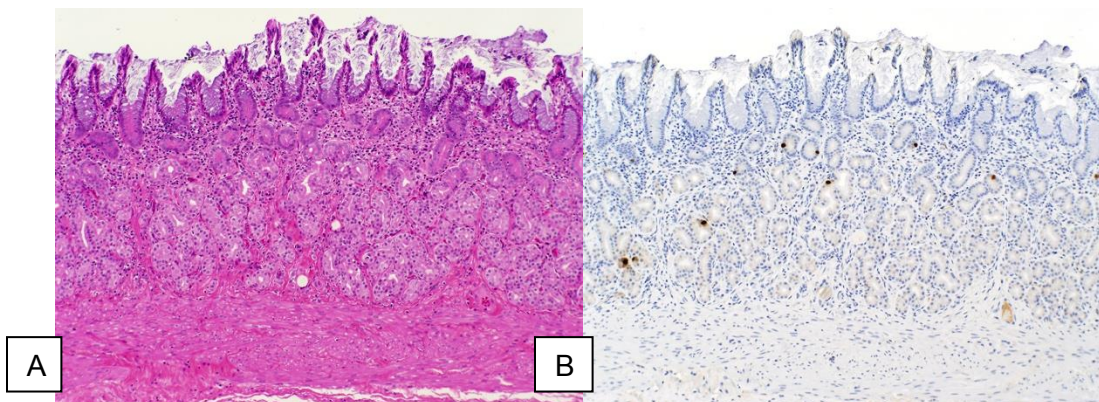


Figure 6. A, Section of gastric fundus from a treatment animal showing well-preserved mucosa with minimal ischemic damage (H&E, x100). B, Immunohistochemical staining for ghrelin from the same area shows a decrease in ghrelin expressing cells (x100).

All treated animals demonstrated minimal changes in the gastric fundus. This confirms that embolization was of adequate extent to induce ischemia, which can be challenging in an organ with an extensive collateral arterial supply. However, on gross pathologic and histopathologic evaluation of the treatment animals, evidence of healing mucosal ulcers was identified in two treated animals, with a healed ulcer identified in one animal. While mucosal ulceration is an unwanted effect, the excellent healing response indicates that the particle embolization-induced ulcers may be mild and transient without significant long-term sequelae.

3.1.4 Limitations of Prior Studies

On three-week endoscopy, ulcers were seen in 2/5 (40%) of our treatment animals. On histopathologic analysis of the gastric mucosa after necropsy, ulcers were seen in 2/6 (33%) treatment animals. Almost all ulcers have been due to non-target embolization since they were seen along the greater curvature and stomach antrum, rather than the gastric fundus, which was embolized.

Interestingly, while all treated animals demonstrated minimal to mild ischemia in the gastric fundus, there was no evidence of mucosal ulceration of the gastric fundus in any

treatment animal. This lack of ulceration is most likely due to the rich collateral vascular supply to the fundus from multiple sources. Considering that all observed ulcers occurred in the lesser curvature and stomach body, this pattern suggests that the injury was related to excessive non-target delivery of embolic material at these locations or could represent ischemic changes from being a “watershed” territory. Histologically, the infused particles were observed throughout the fundus, body, and antrum of the analyzed stomachs, but in highest concentration at the gastric fundus. This suggests that the gastric body may be more sensitive to ischemia than the gastric fundus, which, in addition to the fact that the fundus contains the highest density of ghrelin-expressing cells, further affirms that the fundus is the ideal target for bariatric embolization.(17, 18) Further refinement and understanding of the vascular anatomy to the stomach and a more directed delivery of embolic material to the gastric fundus may reduce the likelihood of developing such gastric ulceration patterns. Considering the critical importance of proton pump inhibitors in the management of gastric and duodenal ulcers, with which ischemia has been implicated as a contributor to pathophysiology, acid reduction may play a role for minimization of ulcer development with bariatric embolization

3.1.5 Summary of Animal Studies

Thus, bariatric arterial embolization significantly suppresses systemic levels of the appetite hormone, ghrelin, and affects weight gain without a compensatory up regulation of ghrelin-expressing cells in the duodenum. In summary, our studies indicate that the gastric fundus can be embolized using minimally invasive endovascular techniques, and results in both a local and a systemic reduction in ghrelin levels with concomitant decrease in weight gain in healthy juvenile swine. Superficial ulcerations were seen in a 33% of treated animals but none of these animals were prospectively treated for ulcer prophylaxis.

3.2 Clinical Studies

3.2.1 Bariatric Embolization of Arteries for the Treatment of Obesity: 30 Day Results from the Initial IDE Study

This study was a prospective single arm study to evaluate the feasibility, safety and toxicity of bariatric embolization in five obese patients. The primary endpoint of this study is weight loss (percentage of excess weight loss [%EWL]) and 30-day Adverse Events.

3.2.1.1 Primary Endpoint (%EWL and Major Adverse Events)

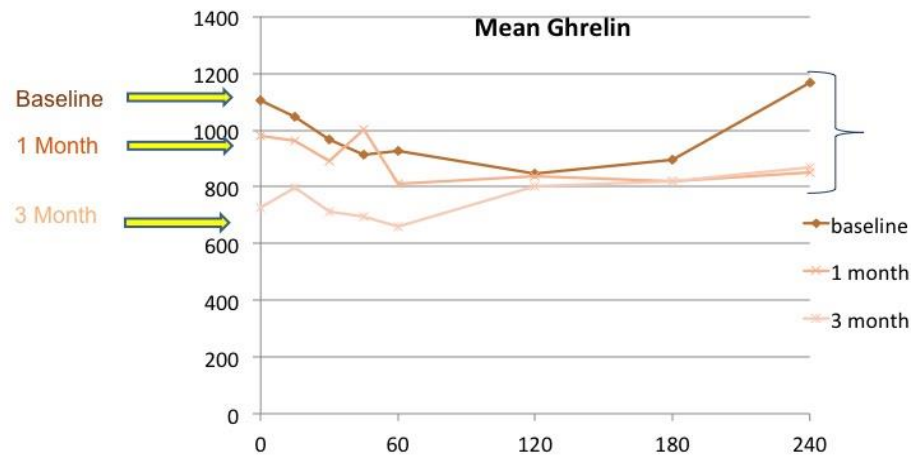
To date, five patients with a mean BMI of 43.8 underwent bariatric embolization at a single institution. All patients tolerated the procedure well and the major adverse event rate at 30 days was 0%. At 30 days, the %EWL was 7.6 % (+/- 3.5).

3.2.1.2 Secondary Endpoints:

At endoscopy, no major gastric ulceration was seen; one patient had a small minor superficial healing ulcer at the fundus. Blanching of the fundus was seen in 40% (2/5 patients). Nausea/vomiting rate was 60% (3/5 patients). Gastric emptying study was normal at baseline and 4 weeks in all patients. Eating and hunger/satiety assessments showed a significant decrease in hunger scores. A summary of the secondary endpoints are shown below:

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Endoscopy 2 wk	Negative	Negative (mild gastritis)	Negative, mild blanching, no ulcers	mild blanching with small superficial ulcer	Mild Blanching No ulcers
Gastric Emptying	Normal	Normal	Normal	Normal	Pending
Lab Changes	None	None	Mildly elevated lipase/amylase	None	None
BP Changes	None	None	None	None	None
Hunger Score	↓ 18	↓ 86%	↓ 26%	Pending	Pending
Nausea/Vomiting	No	No* N: FF/CB	36 hours	N/V for 3-4 hours	N/V – 6 hrs
Abdominal Pain	No	No	Resolved after 36 hours	No	No
Radiation dose (mGy)	4731	4241	4671	6783	4787

To date two patients have had full ghrelin analysis using fasting and meal stimulated time tests (over 240 minutes). As shown below, the baseline ghrelin values have been suppressed at three months and have had blunted response over time after meal stimulation.



3.2.1.3 Non-target Ri R

3.2.1.4 Risk Benefit Analysis

In our initial IDE application, we identified three major areas of risk for bariatric embolization: **Gastric Ulcers, Increased Radiation Dose in Obese Patients and Non Target Vascular Embolization (NTE)**

Gastric Ulcers: In order to mitigate the risks for gastric ulcers, gastroprotective agents were utilized in all patients. In addition, all patients were heavily screened which seemed to adequately identify all patients that would be at higher risk for gastric ulcerations. *Therefore, no major changes will be needed for the protocol.*

Radiation Dose: With radiation dose, the mean dose in this initial study was 5042.6 (+/- 996) mGy. There were no associated skin injuries in any patients at followup clinic visits. However, since this study incorporates cone beam CT to minimize the risk of NTE, this has caused the radiation dose to be slightly higher. We continue to work with imaging vendors to modify fluoroscopic time and using software algorithms to reduce radiation exposure. Furthermore, we anticipate that with added technical experience, we anticipate reductions of fluoroscopic times for these procedures.

NTE: Due to the proximity of the dorsal pancreatic artery to the left gastric and the pancreatico-duodenal arcade to the gastro epiploic, we feel that the risk of

pancreatitis is still one of our biggest concerns. In our trial, 3/5 patients developed significant nausea/vomiting which may be attributable to reflux. To minimize such reflux and NTE, we now routinely dilute the spheres in a larger volume of saline to prevent proximal clumping which can cause reflux. Also, the use of 3D CTA prior to the procedure and conebeam CT was used in all five patients to further understand the vascular anatomy. However due to technical/anatomical challenges, an anti-reflux system was used in only one vessel. Moving forward, the use of anti-reflux systems may still be employed to mitigate NTE to the pancreas.

3.2.1.5 Summary of Initial 5 patient FDA IDE Trial

Bariatric embolization at one month was shown to be safe, effective and well tolerated for the treatment of patients with obesity. Significant decrease in hunger scores were noted at one month.

3.2.2 First in Man presentation at American College of Cardiology

Kipshidze N, A.A., *Endovascular Treatment of Obesity, First in Man* 2013, J Am Coll Cardiol. 2013;61(10_S):. doi:10.1016/S0735-1097(13)62056-2: San Francisco.

Background: Here we provide our preliminary results of the First-In- Man study of Left Gastric Artery Embolization (GAE) safety and efficacy in humans.

Methods: 5 patients with different degrees of obesity underwent GAE with BeadBlock Embolic Bead 300-500µm microspheres (Biocompatibles UK Limited, Chapman House, Farnham Business Park, Weydon Lane Farnham, Surrey, GU9 8QL, UK). Esophagogastrosocopy was performed in all patients before and after GAE and at 1 week follow up to rule out significant initial gastritis or ulcer and any worsening after the procedure. Blood Ghrelin level was also measured before the procedure as well as at 1, 2, 3 and 4 weeks follow up. Observations on Ghrelin levels and patients weight is planned at 3, 6 and 12 month follow up.

Results: There was no case of periprocedural complications. 3 of 5 patients complained about discomfort in epigastrium during first few hours after procedure, but control esophagogastrosocopy did not reveal any impairments. All patients reported decreased appetite during first week after procedure, Weight loss was observed in all patients at 1 month follow up: mean initial weight - 128.12+/- 24.4kg was decreased to 114.8+/- 21.3kg and mean initial Body Mass Index (BMI) - 42.2 +/- 6.8 was decreased to 37.8+/- 5.7. 6 month follow-up results of GAE will be available at time of presentation.

Conclusions: Short term follow up has shown that GAE is safe and feasible. Further studies enrolling larger number of patients are planned to confirm these initial findings.

3.2.2 Retrospective Analysis of Left Gastric Embolization in Patients (Scientific Sessions RSNA Nov 2013)

Gunn, A, Hamilton E. and Oklu, A *Catheter to Curb your Appetite? A Novel Observation of Weight Loss Following Left Gastric Artery Embolization in Humans* 2013, Radiological Society of North America. November 2013; Chicago San Francisco.

PURPOSE

Suppressing serum levels of ghrelin, a neuropeptide with powerful appetite-stimulating effects produced in the gastric fundus, is an intriguing potential means of controlling body weight. Since left gastric artery, which preferentially supplies the gastric fundus, is sometimes embolized in interventional radiology procedures, we assessed post-procedural weight loss in patients after left gastric artery embolization.

METHOD AND MATERIALS

Retrospective analysis of electronic medical records of patients who underwent left gastric artery embolization for upper gastrointestinal (GI) bleeding were compared to age-matched controls of similar patients that had undergone embolization of an artery other than left gastric artery for upper GI bleeding. Patients were included in the analysis if they had a recorded weight within two weeks prior to the embolization and within three months after the procedure. Differences in post-procedural weight loss between the groups were evaluated by a student's t test.

RESULTS

Fifteen patients (mean age: 66.1 years) were included in the experimental group analysis while eighteen patients (mean age: 63.5 years) were included in the control group analysis. The mean pre- and post-procedural weights in the experimental group were 189.1 lbs and 174.5 lbs, respectively, representing a 7.9% decrease in body weight. The mean pre- and post-procedural weights in the control group were 164.7 lbs and 162.8 lbs, respectively, representing a 1.2% decrease in body weight. The post-procedural weight loss of the experimental group was significantly greater than that observed in the control group ($P=0.001$).

CONCLUSION

Patients lose significantly more weight after left gastric artery embolization than following embolization of other arteries for upper GI bleeding. The current data suggests that body weight can be potentially modulated via left gastric artery embolization in humans.

3.3 Bibliography of Published Studies

Bariatric Embolization Preclinical Studies (15, 19-23)

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4 INVESTIGATIONAL PLAN

4.1 Purpose

In this submission, we propose the investigational use of a legally marketed device for a new intended use: the clinical use of the Embosphere Microspheres (Merit Medical, Jordan UT) for bariatric embolization. Thus, this study would be considered physiologic research of the impact of bariatric embolization on the systemic hormonal levels of obesity and its impact on weight gain.

This study is a prospective single arm study to evaluate the feasibility, safety and toxicity of bariatric embolization in 20 obese patients. This study will be performed jointly at two institutions.

The guiding hypothesis of this study is to prospectively test, that transvascular bariatric embolization results in safe and effective weight loss in morbidly obese patients. The duration of the study (time to enrollment of last patient + followup period) will be approximately two years.

Study Objectives and Endpoints

This study will evaluate the feasibility, safety and toxicity of bariatric embolization in 20 morbidly obese patients at week 2 and 1, 3, 6 and 12 months. The primary endpoint of this study is the weight loss (absolute weight change from baseline and the percentage of excess weight loss [%EWL]) and 30 day Adverse Events. Currently five patients have already been enrolled.

Patients will be followed for a period of twelve months and study outcomes will be made by assessment of:

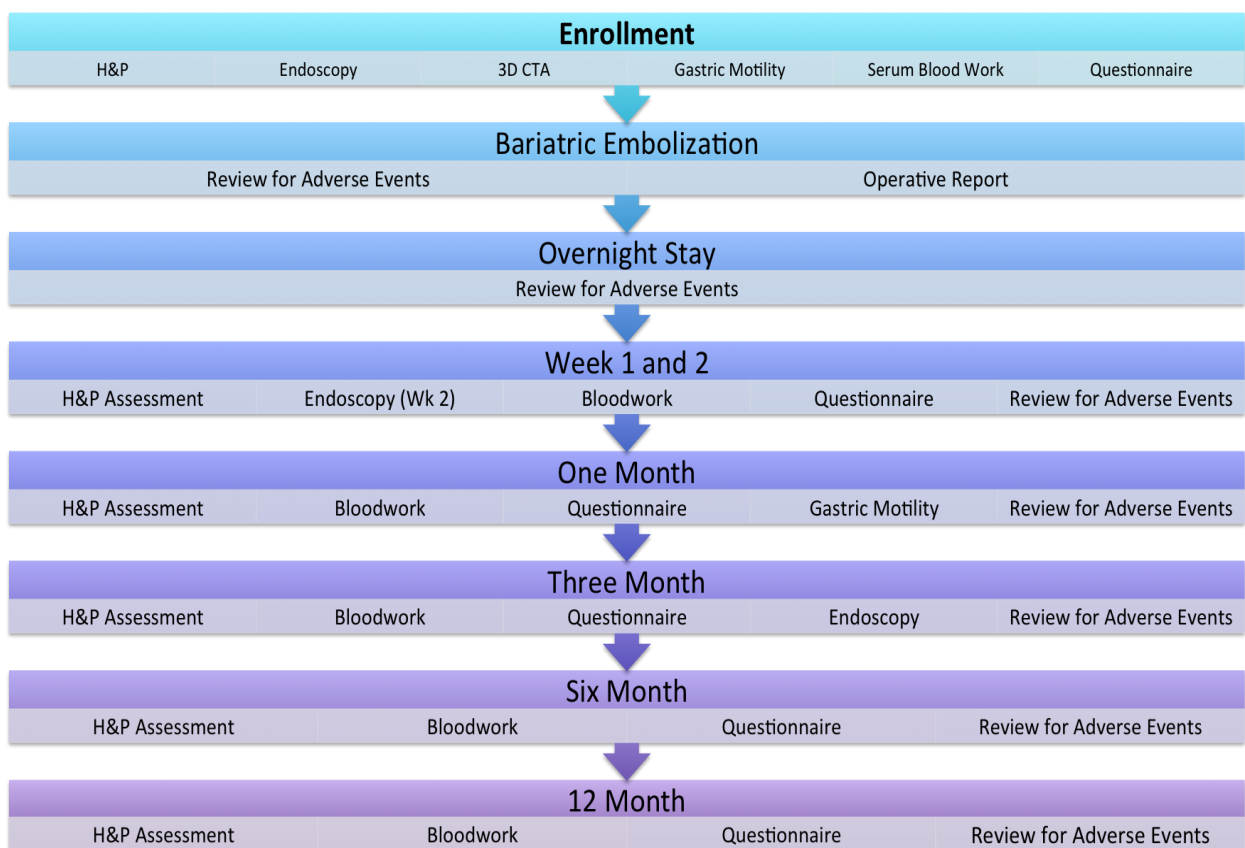
Weight loss	Primary endpoint
30 Day Adverse Events	Primary endpoint
Blood pressure	Secondary endpoint
Lipid Profile	Secondary endpoint
Ghrelin levels	Secondary endpoint
Serum obesity hormones	
Leptin, GLP-1, PYY	Secondary endpoint
Eating and hunger/satiety assessments	
(Three-Factor Eating Questionnaire scores)	Secondary endpoint
Quality of Life Parameters Survey	
SF-36 and IWQOL-Lite	Secondary endpoint
Food Intake	Secondary endpoint
Results from Endoscopy	Secondary endpoint

4.2 Protocol

4.2.1 Study Design

This study is a prospective single arm study to evaluate the feasibility, safety and toxicity of bariatric embolization in 20 obese patients. This study will be performed jointly at two institutions. The guiding hypothesis of this study is to prospectively test, that transvascular bariatric embolization results in safe and effective weight loss in morbidly obese patients

Patients will be evaluated at week 2, and 1, 3, 6 and 12 months following bariatric embolization treatment. A flow chart of the study design is summarized in the following table.



4.2.2 Patient Selection

Subjects who meet the following entrance criteria will provide signed Informed Consent before being enrolled into the study. In all animal studies to date, any form of ulceration/gastritis was visible by week 1 or 2 at follow-up endoscopy. As well, no significant ulceration was seen on any two week (or later) endoscopy on our first five patients and there was no gastric emptying abnormality seen at one month. Therefore, all patients will undergo follow-up endoscopy at week 2 to continue to document procedure safety (see section 4.2.6), but there will be no delay as our additional 15 individual subjects will be enrolled at each site.

4.2.2.1 Inclusion Criteria

- a) Willing, able and mentally competent to provide written informed consent.
- b) Body mass index (BMI) between 35-60.
- c) Residence within 25 miles of the enrolling institution
- d) Vascular anatomy (including celiac, hepatic, and gastric arteries) that in the opinion of the interventional radiologist amenable to Bariatric Embolization, as assessed on 3D CT angiography.
- e) Suitable for protocol therapy as determined by the interventional radiology Investigator.
- f) Adequate hematological, hepatic and renal function as follows:

Hematological	Neutrophils	$> 1.5 \times 10^9/L$
	Platelets	$> 100 \times 10^9/L$
	INR	< 1.5
Hepatic	Bilirubin	$\leq 2.0 \text{ mg/dL}$
	Albumin	$\geq 2.5 \text{ g/L}$
Renal	Estimated GFR	$> 60 \text{ ml/min.1.73m}^2$

- g) Aged 18 years to 70 years.

4.2.2.2 Exclusion Criteria

- a) Prior history of gastric pancreatic, hepatic, and/or splenic surgery
- b) Prior radiation to the upper abdomen
- c) Prior embolization to the stomach, spleen or liver
- d) Portal venous hypertension
- e) Prior or current history of peptic ulcer disease
- f) Large Hiatal Hernia as defined as greater than 5 cm in size.

- g) Significant risk factors for peptic ulcer disease including daily NSAID use and smoking.
- h) Active H. Pylori infection
- i) Weight greater than 400 pound
- j) Known aortic pathology such as aneurysm or dissection renal insufficiency as evidenced by an estimated glomerular filtration rate of < 60 milliliters per minute
- k) Major comorbidity such as cancer, significant cardiovascular disease, diabetes, or peripheral arterial disease.
- l) Complicated arterial anatomic variants including left gastric artery arising from the aorta, and/or hepatic arterial supply via a replaced or accessory left hepatic artery arising from the left gastric artery.
- m) Pregnancy
- n) Preexisting chronic abdominal pain
- o) Postive stool occult study
- p) Abnormal Endoscopy
- q) Abnormal Nuclear Gastric Motility examination
- r) ASA Class 4 or 5 (very high risk surgical candidates: class 4= incapacitating disease that is a constant threat to life) at the time of screening for enrollment into the study will be excluded from participation. This exclusion criterion exists because of the possibility that surgical intervention will be needed if the study intervention subsequently leads to severe adverse effects.
- s) History of Inflammatory Bowel Disease
- t) Autoimmune disease
- u) Cirrhosis
- v) Known history of allergy to iodinated contrast media
- w) Failure to comply with pre-procedure weight management “run-in.”

4.2.2.3 Patient Selection – Screening Methods

CT Scan of the Abdomen with 3D CTA

A contrast enhanced CT scan of the abdomen with 3D CTA will have been completed as a routine work-up investigation prior to Bariatric Embolization

Consideration will be given by the interventional radiologist Investigator to the following eight vessels and their characteristics in their determination of whether a patient possesses vascular anatomy that may be amenable Bariatric Embolization

Eight Mandatory Vessels	Identified (Y/N)	Origin of Artery
Superior mesenteric artery		
Celiac artery		
Common hepatic artery		
Right hepatic artery		
Left hepatic artery		
Right gastric artery		
Left gastric artery		
Gastroduodenal artery		

Screening for Previously Undiagnosed Diabetes

Recruited patients that satisfy the inclusion and exclusion criteria will undergo a preprocedural workup, including a detailed history, physical exam, laboratory studies (including a glucose tolerance test to evaluate for diabetes or pre-diabetes, and H. Pylori serum antibody test)

4.2.3 Pre-Treatment Evaluations and Data Collection

Recruited patients that satisfy the inclusion and exclusion criteria will undergo the following pre-treatment evaluations:

- Detailed medical history by Obesity Specialist
- Physical exam by Obesity Specialist
- Laboratory studies (including a glucose tolerance test, and H. Pylori serum antibody test). These will be performed prior to CTA or endoscopy.)
- Hormone testing using a Meal Tolerance Test
 - The meal tolerance test is administered in order to examine the influence of the gut hormones on glucose tolerance. After the placement of a standard IV catheter and the collection of baseline samples, the subjects are asked to drink Hagen-Daz vanilla ice cream that is put through a blender to get a milkshake consistency, 250 cc (in a cup) is given to the participant. They are asked to drink it within 15 minutes. Samples are drawn at 5', 10', 15', 20', 30', 40', 60', 80', 100', 120', 150', 180' and stored at -80°C in order to measure hormones secreted by the alimentary tract. At each timepoint the subjects will be asked to fill out a simple hunger/satiety scale. Phlebotomy for the meal tolerance test will not exceed 78 mL.
- Upper GI endoscopy
- CT Angiography
- Nuclear gastric motility examination.
- Pregnancy test on the day of or day before procedure.

For the two weeks preceding the procedure, the patients will keep a diet log, and record hunger levels, weight, and symptoms.

The results are acceptable for baseline assessment if they were taken within the **30 day screening period**. The baseline assessments include:

- Medical history and physical examination including height and weight by obesity specialist as a baseline and on all followup visits.
- Hemocult testing
- Hematological and biochemical investigations (performed prior to CTA or endoscopy)
 - Complete blood count (CBC)
 - Liver functions tests (LFTs)
 - Serum albumin
 - Electrolytes, urea, creatinine (EUC)
 - Serum or urine pregnancy tests
 - Fasting chemistries, including glucose and insulin

All patients will be assessed by an obesity specialist who will decide:

1. if the patient can tolerate the procedure
2. there are no absolute contraindications to surgery in the event that surgery becomes necessary to address an adverse event.
3. whether the patient can take omeprazole without causing adverse drug interactions or interrupting treatment with their current medications.
4. All patients will be stratified by standard ASA criteria for surgical risk.
 - a. Patients who are rated by the screening physician (using standard ASA criteria (REF below) as class 4 or 5 (very high risk surgical candidates: class 4= incapacitating disease that is a constant threat to life) at the time of screening for enrollment into the study will be excluded from participation. This exclusion criterion exists because of the possibility that surgical intervention will be needed if the study intervention subsequently leads to severe adverse effects. Class 3 (patient has severe systemic disease that is not incapacitating) or lower-risk patients will not be excluded.
5. Screening for major comorbidities that constitute exclusions from participation in the study will be performed at the time of study entry by careful review of the patient's past medical history and current symptoms and signs by the obesity specialist. Standard diagnostic criteria for diabetes (ADA 2014), symptomatic coronary artery or valvular heart disease, diagnosis of active cancer (except non-melanoma skin cancer), and peripheral artery disease will be used. Referral for further evaluation and treatment will be made as needed.

REF: ADA. Standards of medical care in diabetes- 2014. Diabetes Care 37: Supp 1: S14-S80, 2014

Saklad M. Grading of patients for surgical procedures. Anesthesiol. 1941;2:281-4.

Prior to embolization, patients will have a total of 4 visits with a weight management specialist. After intake a diet plan will be outlined for the patient and patient will be expected to return for 3 more visits over 5 weeks. For the two weeks preceding the procedure, the patients will keep a diet log, and record hunger levels, weight, and symptoms. This series of 4 visits is to be considered the pre procedural "run-in."

All patients will also be assessed by an anesthesia provider prior to the procedure that patient can tolerate conscious sedation and will not be at any additional risk through the use of conscious sedation. Critical Care Nursing staff, as performed with all embolization procedures, will perform all sedation and monitoring. ECG and arterial oxygen saturation will be monitored continuously. Blood pressure and respiratory rates will be measured and recorded every 5 min.

4.2.4 Treatment

4.2.4.1 Medications

The bariatric embolization procedure will be performed with moderate sedation using intravenous midazolam and fentanyl. All patients will take a daily oral proton pump inhibitor (Omeprazole 40 mg) and a daily oral cytoprotective agent (Sucralfate 4g). This regimen is based on clinical management of severe duodenal/gastric ulcers for six weeks.

4.2.4.2 Procedure

The subject will be placed supine on the fluoroscopy table.

Vascular access will be achieved using a small 21 gauge needle then dilated serially over a guidewire to accommodate a 5 French vascular sheath. Using standard catheters, the arteries supplying the fundus arising off the celiac vessel will be selected. Then, a microcatheter will be advanced into the arteries supplying the fundus and small calibrated spheres (300-500 micron size) will be infused until stasis of antegrade arterial flow is achieved, with particular care to avoid infusion of nontarget arteries. Stasis will be defined as visualization of contrast within the target artery for at least 5 cardiac cycles. If an anti-reflux system (Surefire Infusion System) is used, then stasis will be evaluated with the tip collapsed.

Upon completion, the catheters will be removed, and hemostasis will be achieved with manual compression.

The procedure will be performed with an allowable air kerma limit of 4 Gy (4000 mGy). Any patient receiving a greater radiation dose than this will be evaluated for dermal injuries during followup, and if necessary undergo additional evaluation and treatment by a Dermatologist.

4.2.4.3 Patient Monitoring

Real-time monitoring of all patient vital signs will be performed per standard protocol for interventional radiology procedures during the procedure.

4.2.5 Post-Treatment

Patient will be monitored in the post-sedation recovery room for 4 hours until the patient meets usual criteria, followed by overnight hospital admission for observation. If it appears clinically indicated (nausea, vomiting etc) the patient may be admitted for up to 48 hours post procedure.

All decisions to stop the study in any subject, or the study as a whole will be made by a multidisciplinary team. This will include a gastroenterologist, obesity specialist, bariatric surgeon and interventional radiologists. Stopping rules that would necessitate withdrawal of any individual subject, or of the entire study include the development of any of the following conditions during the 6-month period following the procedure in any subject:

1. Development of gastric ulceration at the follow up endoscopy that requires any form of surgical therapy; If ulceration can be managed medically it will be by Dr. Cheskin or Dr. Shin and the patient will remain in the study.
2. Development of any of the following complications will result in stopping the study: small bowel obstruction, hernia, small bowel incarceration, abdominal abscess, gastrointestinal bleed, hypotension, new onset cardiac ectopy, bradycardia, tachycardia, bowel perforation, pneumothorax, pneumonia, hypoxemia, azotemia, heart failure, CO2 narcosis, ventricular bigeminy, pulmonary venous congestion, septicemia, shock, ulcer (anastomotic, peptic), mesenteric venous thrombosis, deep vein thrombosis, pulmonary emboli, adhesions, or death.

4.2.6 Post-Treatment Follow-up

The patient will continue with recording their diet, hunger levels, weight, symptoms (abdominal pain, nausea, cramping, etc) and present for follow up visits at set intervals for physical exam and serum blood tests for ghrelin levels over a 12 month period. By doing so, we will be able to ascertain the effect of bariatric embolization on patient hunger, food intake, symptoms, and serum ghrelin levels in comparison to baseline levels.

The patient will present for clinical follow up with an obesity specialists at week 1-2 and then 1, 3, 6 and 12 month followup. During each visit, the patient log will be recorded. Serum ghrelin testing will be performed. Endoscopic evaluation of the stomach and duodenum will be performed at week 2, and 3 month post-embolization to assess for development of ulcers that may require additional therapy. Hormone testing will be performed using the Meal Tolerance Test as described above in 4.2.3 – except week 1 when only fasting labs will be acquired. At each visit including the 6 month and 1 year followup, patient will be evaluated for symptoms of delayed gastric emptying including post-prandial pain, nausea and vomiting or early satiety.

Patients will also be scheduled to see a weight management specialist after embolization. There will be 16 visits in total with at least one weight management specialist. This will occur during week 1 or 2 and then week 3. From week 4 through 12, the patient will return

every other week. Example: week 4, 6, 8, 10, 12. After week 12, patient will return at least monthly through month 12.

All patients who are women who are able to become pregnant will have a urine pregnancy test prior to their gastric emptying study and endoscopy.

Study Calendar							
	Baseline	Follow-up Assessments: First 30 Days					
	≤ 30 days prior	Day 0:	1-2 week	1 mo	3 mo	6 mo	12 mo
Informed consent	✓						
Demographics	✓						
History and Assessment	✓			✓	✓	✓	✓
Physical exam, incl. - height & weight	✓	✓	✓ (week1)	✓	✓	✓	✓
SF-36 IWQOL Questionnaire	✓		✓(week1)	✓	✓	✓	✓
Hunger Questionnaire	✓		✓(week1)	✓	✓	✓	✓
3D CTA	✓						
Gastric Motility	✓			✓		Optional See 4.2.7	
Endoscopy	✓		✓ (week 2)		✓		
Bariatric Embolization		✓**					
Adverse events		✓	✓	✓	✓	✓	✓
Lab work							
CBC	✓	✓*	✓ Wk 1&2	✓	✓	✓	✓
Hemoccult testing	✓		✓ Wk 1&2	✓	✓	✓	✓
Lipid Profile	✓		✓ Wk 1&2	✓	✓	✓	✓
Ghrelin	✓		✓ Wk 1&2	✓	✓	✓	✓
Leptin, GLP-1, PPY	✓		✓ Wk 1&2	✓	✓	✓	✓
Glucose Tolerance	✓						
Pregnancy test	✓	✓*		✓		✓	
Comp Met Panel	✓	✓*	✓ Wk 1&2	✓	✓	✓	✓
PT/INR	✓	✓*					
APTT/APTT _r	✓	✓*					
Hemoglobin A1c	✓			✓	✓	✓	✓

*These labs will be performed if they are > 30 days old. **Patients may be admitted to the hospital for up to 48 after the embolization procedure if deemed clinically indicated.

* Weight management counseling 4 visits over 5 weeks pre-procedure and 16 more visits post-procedure

4.2.7 Adverse Events

Adverse events such as mortality, serious complications, minor complications and hospital readmission within 30 days of the procedure will be recorded.

Complications (minor or major), were derived under the suggestion of the guidance of the American Society on Metabolic and Bariatric Surgery(34)

Major Complications: Stricture, leak, hematemesis, small bowel obstruction, hernia, small bowel incarceration, gastrointestinal bleed, hypotension, cardiac ectopy, bradycardia, tachycardia, bowel laceration, pneumothorax, pneumonia, hypoxemia, azotemia, heart failure, CO2 narcosis, ventricular bigeminy, pulmonary venous congestion, septicemia, shock, ulcer (anastomotic, peptic), mesenteric venous thrombosis, deep vein thrombosis, pulmonary emboli, hernia, adhesions, and death.

Minor Complications: Gout, nausea and vomiting, dehydration, hypokalemia, hematoma, hypo-/hyperglycemia, ileus, anastomotic edema, elevated hepatic transaminases, gastroparesis, and abdominal abscess.

Additional endoscopy and gastric emptying examination will be performed on any patient who develops symptoms of delayed gastric emptying including post-prandial pain, nausea and vomiting or early satiety during the 1 year follow-up period

All decisions to stop the study in any subject, or the study as a whole will be made by a multidisciplinary team. This will include a gastroenterologist, obesity specialist, bariatric surgeon and interventional radiologists. Stopping rules that would necessitate withdrawal of any individual subject, or of the entire study include the development of any of the following conditions during the 6-month period following the procedure in any subject:

3. Development of gastric ulceration at the follow up endoscopy that requires any form of surgical therapy; If ulceration can be managed medically it will be by Dr. Cheskin or Dr. Shin and the patient will remain in the study.medical /surgical therapy;
4. Development of any of the following complications will result in stopping the study: small bowel obstruction, hernia, small bowel incarceration, abdominal abscess, gastrointestinal bleed, hypotension, new onset cardiac ectopy, bradycardia, tachycardia, bowel perforation, pneumothorax, pneumonia, hypoxemia, azotemia, heart failure, CO2 narcosis, ventricular bigeminy, pulmonary venous congestion, septicemia, shock, ulcer (anastomotic, peptic), mesenteric venous thrombosis, deep vein thrombosis, pulmonary emboli, adhesions, or death.

4.2.8 Subject Removal from the Study

Subjects may be removed from the study by the investigator for the following reasons:

- Staying in the study would be harmful to the subject.
- The subject needs treatment that is not allowed in the study.

- It is decided that another therapeutic approach could improve the subject's medical care.
- The subject fails to follow instructions.
- The subject is not complying with study visits
- The study is cancelled.
- There may be other reasons to remove study subjects that are not known at this time.

4.2.9 Subject compensation.

Patients will receive payments up to \$1200 after Bariatric Embolization using the payment scheme tabulated below:

Week 1-3	Week 4-11	3-5 Months	6-11 Months	12 Months
Food Log \$30	Food Log \$20	Food Log \$20	Food Log \$35	Food Log \$35
Hunger Satiety \$30	Hunger Satiety \$20	Hunger Satiety \$20	Hunger Satiety \$35	Hunger Satiety \$35
Meal Test \$30	Meal Test \$70	Meal Test \$70	Meal Test \$70	Meal Test \$80
Endoscopy \$30	Gastric Emptying \$60	Endoscopy \$70	Gastric Emptying \$60	
Weight Mgmt. (2 visits). \$40	Weight Mgmt. (4 visits) \$80	Weight Mgmt. (3 visits) \$60	Weight Mgmt. (6 visits) \$120	Weight Mgmt. \$20
Basic Labs \$10	Basic Labs \$10	Basic Labs \$10	Basic Labs \$15	Basic Labs \$15
Total \$170	Total \$260	Total \$250	Total \$335	Total \$185

4.3 Scientific Soundness

4.3.1 Study Design

To ensure that data from sites can be pooled, each site will follow the same protocol, which specifies patient selection criteria, treatment procedure, followup requirements, and data collection requirements.

FDA and IRB approvals will be received prior to the implementation of any change to the study protocol that may affect the scientific soundness of the investigation or the rights, safety or welfare of the patients involved in this investigation.

4.3.2 Justification of Sample Size

The purpose of this study is to assess the feasibility and safety of bariatric embolization for the suppression of ghrelin levels to induce weight loss

The results of this study will be used to design future pivotal efficacy studies. The goal will be to recruit 20 patients for statistical analysis.

Given an expected sustained weight loss of 20 lbs, a sample size of 19 patients would give a 80% chance of rejecting the null hypothesis with a P value <0.05 considered statistically significant. Thus, we envision enrolling eventually 20 patients.

4.3.3 Statistical Analysis – Endpoint Assessments

The primary endpoint will be 30 Day Adverse Events and change in weight from baseline. Change in weight will be statistically tested with an analysis of covariance using the baseline weight as the covariate. For each patient, the pre-procedure fasting serum hormonal levels of ghrelin, leptin, glucose, GLP-1, and PYY will be compared to the post-procedural serum levels using the Wilcoxon signed rank test to determine whether there is a statistically significant decrease in any hormonal parameter. Hunger scores and quality of life will be similarly compared.

4.3.4 Data Collection / Case Report Forms

The investigators will record all pre-procedure, procedural, and post-procedure follow-up evaluations and observations including complications and/or adverse effects on the Case Report Forms provided by the Sponsor. All forms when completed will be available for inspection by the Sponsor's representative to verify that all necessary information has been included and reported accurately.

The investigator will retain copies of the Case Report Forms. See appendix A

An Access database located on the Johns Hopkins Radiology Sharepoint site will track study data and patient demographic information. The information will be maintained by study members at both sites as well as the Johns Hopkins weight management professional. The Sharepoint site is secured by the Johns Hopkins School of Medicine Radiology IT Dept.

4.3.5 Adverse Event Reporting

All adverse events: serious (major complications) and non-serious (minor complications) and unanticipated adverse events will be recorded on the CRF by the Research Coordinators. The Data Safety Monitoring Board (DSMB) will review and determine if each adverse event was related to the study. Additionally, adverse events will be reported to the IRBs and FDA, as required.

An investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than ten working days after the investigator first learns of the effect. An investigator shall notify the Sponsor by telephone within 48 hours after the event.

4.3.6 Data Safety Monitoring Board (DSMB)

The DSMB will be composed of a gastroenterologist, bariatric surgeon, an obesity specialist, and an interventional radiologist. The DSMB will meet on a monthly basis in addition to any meetings regarding any specific event. All meetings will be documented and any problems regarding the study protocol will be immediately relayed to the IRB and the FDA. The principal investigators will be responsible for communicating all reports and events to the IRB.

4.4 Risk/Benefit Analysis

4.4.1 Gastric Ulceration from Bariatric Embolization:

To mitigate against gastric ulceration, several technical and clinical approaches will be employed.

Technical approach: In all of our prior animal work, small 50 micron beads were utilized for bariatric embolization. Since smaller beads are known to have a more distal embolic effect, and therefore, the potential for ischemic ulceration will be higher. Currently, arterial embolization with 100-300 micron particles is routinely clinically performed for a number of indications (including embolization of the left gastric artery for control of hemorrhage) and has not shown to have significant clinical sequelae of tissue necrosis or infarction. In fact, all the investigators in this trial have embolized the left gastric artery for gastrointestinal hemorrhages with larger particles (100-300 micron) and have not seen any cases of gastric ulceration/perforation. Limited clinical experience with bariatric embolization has been performed with larger bead sizes. Therefore, based upon the limited clinical experience and our pre-clinical data, bariatric embolization with 400 micron will be performed.

Clinical methods: In addition to these technical changes, all patients will be aggressively prescreened for gastric ulcerations including the use of gastric motility examinations, baseline upper endoscopy and baseline CT angiography. Furthermore, as shown in our exclusion criteria, patients that are considered higher risk for ulcerations will be excluded:

Exclusion criteria:

- prior history of gastric pancreatic, hepatic, and/or splenic surgery
- Prior radiation to the upper abdomen
- Prior embolization to the stomach, spleen or liver
- Portal venous hypertension
- Prior history of peptic ulcer disease
- Significant risk factors for peptic ulcer disease including daily NSAID use and smoking.
- Active H. pylori infection

Finally, to further improve the safety profile of this procedure, gastroprotective agents such as oral proton pump inhibitor (omeprazole) and Sucralfate will be utilized. Clinical use of proton pump inhibitors (PPI) has significantly influenced the management of acid-peptic disorders dramatically over the last decade. Three of these agents are now widely available; omeprazole (available since 1989), lansoprazole (1995), and pantoprazole (1997). These agents selectively and irreversibly inhibit the gastric hydrogen/potassium adenosine triphosphatase (H⁺/K⁺-exchanging ATPase), part of the 'proton pump' that is

involved in the final acid secretory process. They thereby inhibit both basal and stimulated secretion of gastric acid of parietal cells. Clinical uses include the treatment of peptic ulcer disease, gastroesophageal reflux disease, Barrett's esophagus, Zollinger-Ellison Syndrome, and the eradication of *Helicobacter pylori* as part of combination regimens. In addition, another typical agent used for ulcer healing is Carafate. This agent works by forming a coating over ulcers, protecting the area from further injury.

Therefore, the use of a both systemic therapies such as PPI and a local mucosal agent (Carafate) will provide a protective mechanism to the gastric mucosa to minimize gastric ulceration. Not only do these agents prevent ulcer formation but also have been shown to also improve the healing rates of gastric and duodenal ulcers. Oral proton pump inhibitor (Omeprazole 40 mg) and a daily oral cytoprotective agent (Sucralfate 4g) will be taken for two weeks prior and six weeks after the procedure in order to protect against gastric ulcers.

4.4.2 Increased Radiation Dose in Obese Patients

Based upon the pre-IDE discussions, the procedure will be limited to a cumulative air kerma to 4 Gy (4000 mGy). This proposed limit is below the trigger point recommended for followup of patients for skin injuries recommended by NCRP Report No. 168 (5 Gy), and well above the mean dose of 2367 mGy for treatment of gastrointestinal hemorrhage with interventional radiology techniques reported in a multicenter study(35). Furthermore, we are currently in discussion with imaging vendors to provide the latest imaging software algorithms that provide ultra low dose imaging during angiography. Systems with these capabilities can reduce radiation up to 60%. Examples of such systems include the Siemens Artis Q.zen or the Philips Clarity IQ technology product line. When possible, such systems will be utilized.

4.4.3 Non target vascular embolization

Because of the variable vascular supply of the stomach and the shared arterial supply with other surrounding vital organs, such as the diaphragm, esophagus, liver, spleen, and pancreas, there is concern for non target embolization (NTE) due to reflux. In our preclinical animal studies, there was evidence of non-target injury to the body and antrum of the stomach due to vascular reflux of embolic spheres. Because patients who would benefit from BAE are generally healthy aside from their obesity, NTE (from either poor targeting or reflux) is unacceptable. To mitigate this NTE three specific technical methods will be implemented:

- a) 3D CT Angiography: Prior to the procedure all patient will undergo a 3D CT angiography to not only identify patients with aberrant vascular anatomy but also to assess the vasculature to the gastric fundus, antrum and associated adjacent organs such as the pancreas, liver and spleen.
- b) Cone Beam Computed Tomography (CBCT): Utilization of CBCT provides near real time three-dimensional (3D) maps of the gastric and adjacent organ arterial supply and CT-like soft tissue contrast, to enable precise targeting to the gastric fundus and avoid NTE of nearby critical organs.

- c) Anti-reflux infusion microcatheters: Finally, if feasible, the use of an anti-reflux microcatheter (Surefire Medical, Westminster, CO) will be utilized to perform all embolizations to eliminate NTE and provide precise targeting of the gastric fundus.

4.4.4 Potential Benefits and Study Justification

The purpose of this study is to investigate the feasibility and safety of bariatric embolization for suppression of ghrelin levels to induce weight loss. There is no guarantee of specific benefit to the patients enrolled in this study.

Data collected in this clinical investigation will provide a foundation for future efficacy studies.

4.5 Administrative and Regulatory Considerations

4.5.1 IRB Review

The investigator will provide the Sponsor with documentation that the IRB has approved the protocol and informed consent form prior to initiating the trial.

4.5.2 Informed Consent

Informed consent will be obtained from the subject prior to enrollment in this study.

The informed consent form will conform to 21 CFR 56 and will contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of the study and that the subject is free to withdraw from the study at any time. The subject will have the opportunity to ask questions and be given time for consideration.

A copy of the signed informed consent will be maintained and available for review by the Sponsor and their designated monitor.

The investigator is responsible to ensure that informed consent is obtained from each subject and for obtaining the appropriate signatures and dates on the consent form. The subject should retain a copy of the signed informed consent.

4.5.3 Confidentiality

All information regarding patient identification will be kept confidential. This information may be audited by the sponsor and regulatory authorities, and may be inspected and/or copied.

Each patient will be assigned a study number. Study info will be kept in a locked room with access limited to individuals participating in the study. In addition, all data will be digitally encrypted.

All data will be stored on PI's and research coordinator's computer with digital encryption for 2 years. Only the primary, co-investigators and research coordinator will have access to the data. The PI will be responsible for receipt and transmission of all data.

All data will be de-identified and stored on a computer with password protection and digital encryption of all data on the hard drive.

4.5.4 Monitoring

4.5.4.1 Monitor

This study will be monitored by an independent person designated by the sponsor, to ensure that the trial is conducted in accordance with the protocol, the signed investigator's agreement, the requirements of 21 CFR 812, and any other conditions of approval imposed by the reviewing IRBs and/or FDA.

The monitor for the study will be:

Lawrence J Cheskin, MD
Director of Johns Hopkins Weight Management Center HBS
550 North Broadway, Suite 1001
Baltimore , Maryland 21205

4.5.4.2 Monitoring Procedures

Selection of the Monitor

The Monitor is designated by the Sponsor to oversee the investigation. The Monitor will be qualified by training and experience to monitor the investigational study in accordance with all applicable regulations.

General Duties of the Monitor

The monitor must ensure that the investigation is conducted in accordance with the following:

1. The signed investigator agreement;
2. The investigational plan;
3. Any conditions imposed by the IRB or FDA;
4. The requirements of the IDE regulations (45 FR January 18, 1980, Pp. 8942-8980, or 21 CFR Part 812) and other applicable regulations.

Reports by the Monitor to the Sponsor

1. Any noncompliance with the items listed above shall be reported to the Sponsor. In the event that the investigator is not complying with the requirements outlined above, it is the sponsor's responsibility to secure compliance.
2. Any unanticipated adverse device-related effects shall be reported.

Initiating the Study

Prior to initiating the investigation plan, the monitor must conduct a pre-investigational visit with each investigator to ensure the following:

1. The investigator understands and accepts his/her obligation in conducting the clinical investigation.
2. The investigator and his/her staff have sufficient time and access to an adequate number of subjects to conduct the clinical investigation.
3. The investigator has a signed investigator agreement and CV on file.

4. Each IRB approval is on file, and all conditions of the IRB approval have been met.
5. The clinical investigation does not begin until FDA notifies the Sponsor in writing that the study is approved.

During the Course of the Investigation

1. Conduct periodic discussions with the investigator and his/her staff to ensure that the study is being conducted in accordance with the protocol or investigational plan, any conditions of the IRB, and the requirements of the IDE regulations.
2. Review case report forms and records to ensure that they are complete, accurate and legible.
3. Review source medical records and case report forms for any serious or unanticipated adverse effects.

F. Records of the Monitor

The monitor shall prepare and maintain records of each pre-investigational and each periodic visit or discussion. These records will include the following information:

1. Date, name, and address of the investigator, and names of other staff members present at each meeting.
2. A summary of the findings of the visit.
3. A statement of any action taken by the monitor or investigator to correct any deficiencies noted.
4. The monitor shall immediately notify the Sponsor of any conditions of noncompliance with the protocol, investigational plan, conditions of the IRB or FDA approval, or the IDE regulations.

4.5.5 Compliance

The Sponsor will monitor compliance to the protocol and appropriate regulations. The investigator will not implement any deviation from or add any changes to the protocol without agreement by the Sponsor, and prior review and documented approval from the FDA and appropriate IRB, except when necessary to eliminate any hazard to trial subjects. If compliance is not obtained, the Sponsor reserves the right to terminate the investigator's participation in the trial or to terminate the trial itself.

4.5.6 Training/ Investigator Qualifications

All investigators will be qualified Interventional Radiologists experienced in the performing embolization procedures with the subject devices. Additionally, the investigators will be trained in the protocol, and data collection and record retention requirements.

4.5.7 Records Retention

The investigator will retain study records for a period of 2 years following the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. The Sponsor is to be notified prior to the destruction of any study records.

5 METHODS, FACILITIES, AND CONTROLS USED FOR MANUFACTURING

The legally marketed Embosphere Microspheres (Merit Medical, Jordan UT) will be used to complete the bariatric embolization procedures described in the investigation plan.

As this is an Investigator-sponsored IDE, only commercially available Embosphere Microspheres, supplied by the manufacturer, will be used in this study.

6 INVESTIGATORS

6.1 List of Investigators

The investigators identified for participation in the study are:

Principal Investigator:

Aravind Arepally, M.D., FSIR
1984 Peachtree Road
Suite 505
Atlanta, Georgia 30309

Co-Principal Investigators:

Clifford R. Weiss, M.D
Interventional Radiology Center
Department of Radiology
1800 Orleans Street
The Johns Hopkins Hospital
Sheikh Zayed Tower, Suite 7203
Baltimore, MD 21287

Dara L. Kraitchman, V.M.D., Ph.D.,
F.A.C.C.
Cardiovascular
Interventional Section Head
Division of MR Research
Russell H. Morgan Department of
Radiology and Radiological Science
Johns Hopkins University
600 N. Wolfe Street
Park Building 314
Baltimore, MD 21287

Aaron Fischman MD
Asst. Professor of Radiology and
Surgery
1 Gustave Levy Place
Box 1234, Dept. of Radiology
Icahn School of Medicine at Mount
Sinai
New York, NY 10029

Rahul Patel MD
Asst. Professor of Radiology and
Surgery
1 Gustave Levy Place
Box 1234, Dept. of Radiology
Icahn School of Medicine at Mount
Sinai
New York, NY 10029

6.2 Agreement and Certification

Prior to participating in the study all investigators will sign an Agreement to adhere to the protocol and to fulfill other responsibilities as defined in the FDA regulations or in the Investigator Agreement.

The Sponsor certifies that all of the investigators who will take part in this study will read and sign the Agreement of Investigator's Responsibilities before participating in the study. No investigator will participate in the investigation until they have signed the Agreement.

A copy of the Investigator Agreement is included as Attachment 6A.

Attachment 6A -Investigator Agreement

The investigator will provide financial information for up to one year following the study per 21 CFR 812.43(c)(5).

CLINICAL INVESTIGATOR AGREEMENT

Feasibility and Safety Study:

Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss

I, _____, agree to participate as a Principal Investigator in the clinical investigation: Feasibility and Safety Study: Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss

I agree and/or certify that:

1. I will conduct the clinical investigation in accordance with this agreement, all requirements of the investigational plan, IDE regulations, other applicable regulations of the FDA, and any conditions of approval imposed by my reviewing Institutional Review Board (IRB) or FDA. I agree to abide by all of the responsibilities of Investigators addressed under [21 CFR Part 812](#), Subpart E and Subpart G, including but not limited to the following:
 - a. I will obtain written approval from the authorized IRB for the institution at which this investigation will be conducted. If I am not also the sponsor-investigator of the corresponding IDE application, I will submit the certification of IRB approval and any conditions of this approval to the sponsor.
 - b. I will ensure that Informed Consent is obtained from each subject participating in this clinical investigation in accordance with the informed consent regulation found in [21 CFR Part 50](#), and that a signed copy of the informed consent is available to the sponsor and the sponsor's designated monitor.
 - c. I will supervise all testing of human subjects under this protocol and will allow only those physician co-investigators listed on the last page of this agreement to administer this devices and/or perform follow-up medical evaluations on the device.
 - d. I will ensure the accurate completion of protocol case report forms and, if I am not also the sponsor-investigator of the corresponding IDE application, I will submit completed protocol case report forms, progress reports, and a final report to the sponsor at the time frames specified in the Protocol and/or FDA regulations.
 - e. I will direct the retention of required records and documents related to the investigation.
2. I have the appropriate, relevant qualifications to conduct and to oversee the conduct of the clinical investigation as documented by the following: (*Check applicable statement*)

____ My relevant qualifications, including dates, location, extent, and type of experience, are listed in my most recent curriculum vitae (CV), which is attached to this Agreement and which will be maintained by the sponsor (sponsor-investigator) of the corresponding IDE application.

____ My curriculum vitae (CV) does not reflect my relevant qualifications, therefore attached to this Agreement is a statement of my relevant experience (including dates, location(s), extent, and type of experience), which will be maintained by the sponsor (sponsor-investigator) of the corresponding IDE application.
3. There are no reasons to question my ability to oversee the appropriate conduct of this clinical investigation. (*Check applicable statement.*)

- _____ I have never participated in an investigation or other research activity, which was terminated (disqualified) by FDA, the IRB (or equivalent), or sponsor of a study due to a non-compliance issue.
- _____ I have participated in an investigation or other research activity, which was terminated (disqualified) by FDA, the IRB (or equivalent), or sponsor of a study due to a non-compliance issue. The specific circumstances leading to this termination and my role in the respective problems or issues and the resolution of these problems or issues are summarized in an attachment to this Agreement.
4. I further certify that I have not been debarred under the Generic Drug Enforcement Act of 1992, 21 USC §§ 335a and 335b. In the event that I become debarred or receive notice of an action or threat of an action with respect to my debarment during the term of this Agreement, I agree to immediately notify the sponsor (sponsor-investigator) and the authorized IRB for my study site. If I am the sponsor-investigator of the corresponding IDE application I will notify the authorized IRB for my study site and the FDA.
5. As required by [21 CFR Part 54](#), I will obtain sufficient accurate financial disclosure information from all investigators that participate in this clinical investigation in order to submit a complete and accurate certification or disclosure statement. The investigator will provide financial information for up to one year following the study per 21 CFR 812.43(c)(5).

PRINCIPAL INVESTIGATOR

Name of Principal Investigator (please print or type)

Office (Mailing Address)

City/State/Zip

E-mail

Telephone

FAX

Signature of Principal Investigator

Date

Sub-INVESTIGATORS: (i.e., research fellows, residents, associate) who will be assisting the investigator in the conduct of the investigations.

Name of the Sub-Investigator (please print or type)

Signature

Date

7 INSTITUTIONAL REVIEW BOARDS AND CERTIFICATION

The clinical study will be conducted at a maximum of 3 clinical sites. The address and chairmen of the institutional review boards of the currently identified sites are given below:

Jeffrey Silverstein, MD, CIP
Executive Director; IRB Chair
Program for Protection of Human Subjects
Icahn School of Medicine
One Gustave L. Levy Place
Box 1081
New York, NY 10029-65749
Tel: 212-824-8200
E-mail: jeff.silverstein@mssm.edu

Howard Lederman M.D., Ph.D.
Johns Hopkins Medical Institutes
East Baltimore Campus (Central Office)
1620 McElderry St., Reed Hall - B130, Baltimore, MD 21205-1911

The investigational plan has not yet been submitted to any institutional review boards. The Sponsor certifies that the study will not begin at any site until the FDA IDE approval and IRB approval has been obtained.

8 PROMOTION

The legally marketed Embosphere Microspheres (Merit Medical, Jordan UT) will be used to complete the bariatric embolization procedures described in the Investigational Plan.

This is an Investigator-sponsored clinical investigation. The Sponsor-Investigator and Principal Investigators will not promote the device for the investigational use which is the subject of this Investigational Device Exemption.

There will be no charge to the patient for the investigational device during the study.

9 ENVIRONMENTAL ANALYSIS REPORT

The legally marketed Embosphere Microspheres (Merit Medical, Jordan UT) will be used to complete the bariatric embolization procedures described in the Investigational Plan.

The Sponsor-Investigator claims that this application for an Investigational Device Exemption is exempt from the requirement to prepare an Environmental Impact Analysis.

10 LABELING

This is an Investigator-sponsored investigation of the legally-marketed Embosphere Microspheres (Merit Medical, Jordan UT).

No changes will be made to the labeling by the Sponsor-Investigator. All beads that are obtained from the manufacturer will label the study inventory by the research coordinator:

Caution: Investigational Device. Limited by Federal law to investigational use.*

*Applies to use of this device in the study: "Feasibility and Safety Study: Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss"

11 INFORMED CONSENT DOCUMENTS

Patients will be provided with a full explanation, in lay terms, of the aims of the study and the potential benefits as well as the possible side effects and risks involved. It will be explained that they may refuse to take part in, or withdraw from the study without prejudice to their future care and treatment.

Written informed consent must be obtained from all patients prior to study entry. The consent form must be filed in the patient record. Consent to participate in this study will be obtained from the patient both verbally and in writing. In the case where the patient is not fluent in English an interpreter must be present during the obtaining of consent. Patients will be issued with a copy of the information provided and their consent to participate in the study. All informed consent forms used in this study must be approved by the relevant IRB and by the study Sponsor.

A copy of the model Informed Consent Document can be found in Appendix B.

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APPENDIX A- CASE REPORT FORMS

Feasibility and Safety Study: Bariatric Embolization for Suppression of Ghrelin Level to Induce Weight Loss

Center: ☐ Johns Hopkins ☐ Mt. Sinai

Patient number _____ Patient initials _____

Screening information

Informed consent signed? ☐ Yes ☐ No Date of informed consent _____

Inclusion Criteria

NB: A response of “no” means that the patient is **not eligible** for this study

- | | Yes | No |
|---|--------------------------|--------------------------|
| a. Willing, able, and mentally competent to provide written informed consent | <input type="checkbox"/> | <input type="checkbox"/> |
| b. Body mass index (BMI) between 40-60 | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Residence within 25 miles of the enrolling institution | <input type="checkbox"/> | <input type="checkbox"/> |
| d. Hepatic vascular anatomy that in the opinion of the interventional radiologist amenable to Bariatric Embolization, as assessed on 3D CT angiography. | <input type="checkbox"/> | <input type="checkbox"/> |
| e. Suitable for protocol therapy as determined by the interventional radiology Investigator. | <input type="checkbox"/> | <input type="checkbox"/> |
| f. Adequate hematological, hepatic and renal function as follows: | | |
| Neutrophils > 1.5 x 10 ⁹ /L | <input type="checkbox"/> | <input type="checkbox"/> |
| Platelets > 100 x 10 ⁹ /L | <input type="checkbox"/> | <input type="checkbox"/> |
| Bilirubin ≤ 2.0 mg/dL | <input type="checkbox"/> | <input type="checkbox"/> |
| Albumin ≥ 2.5 g/L | <input type="checkbox"/> | <input type="checkbox"/> |
| Estimated GFR> 60ml/min.1.73m ² | <input type="checkbox"/> | <input type="checkbox"/> |
| INR<1.5 | <input type="checkbox"/> | <input type="checkbox"/> |
| g. Age 18 years to 70 years. | <input type="checkbox"/> | <input type="checkbox"/> |

Exclusion Criteria

NB: A response of “yes” means that the patient is **not eligible** for this study

	Yes	No
a. Prior history of gastric pancreatic, hepatic, and/or splenic surgery	<input type="checkbox"/>	<input type="checkbox"/>
b. Prior radiation to the upper abdomen	<input type="checkbox"/>	<input type="checkbox"/>
c. Prior embolization to the stomach, spleen or liver	<input type="checkbox"/>	<input type="checkbox"/>
d. Portal venous hypertension	<input type="checkbox"/>	<input type="checkbox"/>
e. Prior history of peptic ulcer disease	<input type="checkbox"/>	<input type="checkbox"/>
f. Large Hiatal Hernia, greater than 5 cm.		
g. Significant risk factors for peptic ulcer disease including daily NSAID use and smoking.	<input type="checkbox"/>	<input type="checkbox"/>
h. Active H. Pylori infection	<input type="checkbox"/>	<input type="checkbox"/>
i. Weight greater than 400 pounds	<input type="checkbox"/>	<input type="checkbox"/>
j. Known aortic pathology such as aneurysm or dissection renal insufficiency as evidenced by an estimated glomerular filtration rate of < 60 milliliters per minute	<input type="checkbox"/>	<input type="checkbox"/>

k. Major comorbidity such as cancer, significant cardiovascular disease, diabetes, or peripheral arterial disease.	<input type="checkbox"/>	<input type="checkbox"/>
l. Complicated arterial anatomic variants including left gastric artery arising from the aorta, and/or hepatic arterial supply via a replaced or accessory left hepatic artery arising from the left gastric artery.	<input type="checkbox"/>	<input type="checkbox"/>
m. Pregnancy	<input type="checkbox"/>	<input type="checkbox"/>
n. Preexisting chronic abdominal pain/discomfort	<input type="checkbox"/>	<input type="checkbox"/>
o. Positive stool occult study	<input type="checkbox"/>	<input type="checkbox"/>
p. Abnormal Endoscopy	<input type="checkbox"/>	<input type="checkbox"/>
q. Abnormal Nuclear Gastric Motility examination	<input type="checkbox"/>	<input type="checkbox"/>
r. ASA Class 4 or 5	<input type="checkbox"/>	<input type="checkbox"/>
s. History of Inflammatory Bowel Disease	<input type="checkbox"/>	<input type="checkbox"/>
t. Autoimmune Disease	<input type="checkbox"/>	<input type="checkbox"/>
u. Cirrhosis	<input type="checkbox"/>	<input type="checkbox"/>
v. Known history of allergy to iodinated contrast media	<input type="checkbox"/>	<input type="checkbox"/>

Baseline Visit

Date of visit: _____

Age	
Gender	<input type="checkbox"/> Male <input type="checkbox"/> Female
Ethnicity	<input type="checkbox"/> White / Caucasian <input type="checkbox"/> Black / African American <input type="checkbox"/> Hispanic / Latino <input type="checkbox"/> Asian <input type="checkbox"/> Other, specify _____
Height	
Weight	
Body mass index	
Blood pressure	
Heart rate	
If female, has a pregnancy test been performed?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
If yes, date of test	
If yes, pregnancy test result	<input type="checkbox"/> Negative <input type="checkbox"/> Positive (ineligible)
Prior weight-loss attempts:	<input type="checkbox"/> Diet <input type="checkbox"/> Exercise regimen <input type="checkbox"/> Medications, list: _____ <input type="checkbox"/> Psychotherapy

Physical Examination

Date of exam:
 d d m m m y y

Body System	Check One			Specify any abnormalities
	Not Done	Normal	Abnormal	
Dermatological	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
HEENT/Neck	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Respiratory	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Cardiovascular	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Gastrointestinal/ Digestive	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Genitourinary	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Neurological	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Musculoskeletal	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Endocrine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Haematologic/ Lymphatic	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Metabolic/ Nutritional	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
General Appearance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Medical and Surgical History / Current Conditions

Date of assessment:

d	d	m	m	m	y	y

Please list below next to the appropriate body system code and indicate if condition is past (not currently active) or current (ongoing). Please include surgery dates if appropriate.

Body System Codes

1 – Dermatological	4 – Cardiovascular	7 – Neurological	10 – Haematologic/Lymphatic	13 – Other, specify
2 – HEENT/Neck	5 – Gastrointestinal	8 – Musculoskeletal	11 – Metabolic/ Nutritional	
3 – Respiratory	6 – Genitourinary	9 – Endocrine	12 – Psychiatric	

[illegible]

Baseline laboratory analysis

Date performed

Test	value	required range	meets criteria?
Hematocrit			
White Blood Cell Count			
Neutrophil count		$> 1.5 \times 10^9/\text{L}$	<input type="checkbox"/> yes <input type="checkbox"/> no
Platelet count		$> 100 \times 10^9/\text{L}$	<input type="checkbox"/> yes <input type="checkbox"/> no
AST			
ALT			
Bilirubin		$\leq 2.0 \text{ mg/dL}$	<input type="checkbox"/> yes <input type="checkbox"/> no
Albumin		$\geq 2.5 \text{ g/L}$	<input type="checkbox"/> yes <input type="checkbox"/> no
Sodium			
Potassium			
Chloride			
BUN			
Creatinine			
Estimated GFR		$> 60 \text{ mL/min.1.73m}^2$	<input type="checkbox"/> yes <input type="checkbox"/> no
Glucose			
Insulin			
Serum Ghrelin			
Serum Leptin			
Serum GLP-1			
Serum PPY			
Total cholesterol			
Low-density lipoprotein			
High-density lipoprotein			
Triglyceride level			
Glucose tolerance			

Baseline contrast-enhanced 3D CTA

Date performed _____

Eight Mandatory Vessels	Identified (Y/N)	Origin of Artery
Superior mesenteric artery		
Celiac artery		
Common hepatic artery		
Right hepatic artery		
Left hepatic artery		
Right gastric artery		
Left gastric artery		
Gastroduodenal artery		

Baseline endoscopy

Date performed _____

Findings	
Gastritis?	<input type="checkbox"/> no <input type="checkbox"/> yes –location:
Ulcers?	<input type="checkbox"/> no <input type="checkbox"/> yes –location:
Other findings:	(list)

Baseline gastric motility

Date performed _____

Transit time: _____

Baseline hunger survey

Date performed _____

Hunger score: _____

Bariatric embolization procedure

Date performed

Findings	
Technical success?	<input type="checkbox"/> yes <input type="checkbox"/> no
Contrast volume used	
Radiation dose	
Periprocedural complications?	<input type="checkbox"/> yes <input type="checkbox"/> no If yes, please describe:
Use of Surefire Infusion System	<input type="checkbox"/> yes <input type="checkbox"/> no
Target Vessel Stasis	<input type="checkbox"/> yes <input type="checkbox"/> no
Volume of Beads used	

Vessel Embolizaed	<input type="checkbox"/> Left Gastric <input type="checkbox"/> Gastroepiploic <input type="checkbox"/> Other :
Target Vessel Stasis	<input type="checkbox"/> yes <input type="checkbox"/> no
Volume of Beads used	
Use of Surefire Infusion System	

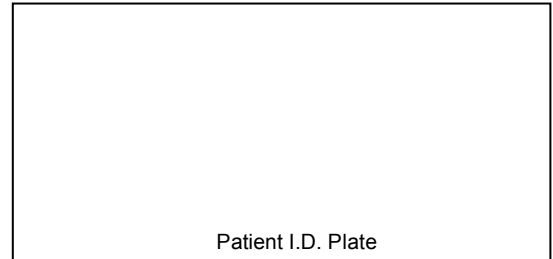
Vessel Embolizaed	<input type="checkbox"/> Left Gastric <input type="checkbox"/> Gastroepiploic <input type="checkbox"/> Other :
Target Vessel Stasis	<input type="checkbox"/> yes <input type="checkbox"/> no
Volume of Beads used	
Use of Surefire Infusion System	

Vessel Embolized	<input type="checkbox"/> Left Gastric <input type="checkbox"/> Gastroepiploic <input type="checkbox"/> Other :
Target Vessel Stasis	<input type="checkbox"/> yes <input type="checkbox"/> no
Volume of Beads used	
Use of Surefire Infusion System	

Follow-up visit	
Interval	<input type="checkbox"/> 1month <input type="checkbox"/> 3month <input type="checkbox"/> 6 month <input type="checkbox"/> 12 month
Ethnicity	<input type="checkbox"/> White / Caucasian <input type="checkbox"/> Black / African American <input type="checkbox"/> Hispanic / Latino <input type="checkbox"/> Asian <input type="checkbox"/> Other, specify _____
Weight	
Body mass index	
Blood pressure	
Heart rate	
Endoscopy results	<input type="checkbox"/> negative <input type="checkbox"/> gastritis <input type="checkbox"/> ulcers
Gastric motility time	
Hunger score	
Compliant with omeprazole and sucralfate?	<input type="checkbox"/> yes <input type="checkbox"/> no
Lab results	
Glucose tolerance	<input type="checkbox"/> Negative <input type="checkbox"/> Positive (ineligible)
Serum Ghrelin	
Serum Leptin	
Serum GLP-1	
Serum PPY	
Total cholesterol	
Low-density lipoprotein	
High-density lipoprotein	
Triglyceride level	
Glucose tolerance	

Adverse Event (AE) Report	
Adverse event type	<input type="checkbox"/> mortality <input type="checkbox"/> major complication <input type="checkbox"/> minor complication
Adverse event description	
AE start date	
AE stop date	
Action taken?	<input type="checkbox"/> Continued study protocol <input type="checkbox"/> Study protocol altered <input type="checkbox"/> Study protocol terminated
Treatment given?	<input type="checkbox"/> None <input type="checkbox"/> Medications, specify <input type="checkbox"/> Other, specify:
Outcome	<input type="checkbox"/> Resolved w/sequelae <input type="checkbox"/> Resolved, no sequelae <input type="checkbox"/> Ongoing <input type="checkbox"/> Death
Is event related to bariatric embolization?	<input type="checkbox"/> No <input type="checkbox"/> Unlikely <input type="checkbox"/> Possible <input type="checkbox"/> Probable <input type="checkbox"/> Definite
Periprocedural complications?	<input type="checkbox"/> yes <input type="checkbox"/> no If yes, please describe:

APPENDIX B- DRAFT INFORMED CONSENT DOCUMENT



12 RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **Safety and Feasibility of Bariatric Embolization for
Suppression of Ghrelin Level to Induce Weight Loss**

Application No.: **xxxxxx**

Sponsor: **XXXXX**

Principal Investigator:

Aravind Arepally, M.D., FSIR
Physical Address:
Division of Interventional Radiology, Piedmont Healthcare
1984 Peachtree Road, Suite 505
Atlanta, Georgia 30309
Phone: 404-561-6153

1. What you should know about this study:

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Please ask questions at any time about anything you do not understand.

- You are a volunteer. If you join the study, you can change your mind later. You can decide not to take part or you can quit at any time. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.
- Ask your study doctor or the study team to explain any words or information in this informed consent that you do not understand.
- For clinical trials: A description of this clinical trial will be available at www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search the Web site at any time.
- If you have clinical tests done as part of this research study, a statement will be added to your medical record that you are in this research study. Results from any clinical tests you have will be included in your medical record. Doctors outside of this research institution may not have access to this information. You can ask the research team to send this information to any of your doctors.

2. Why is this research being done?

The purpose of this study is evaluate the safety and feasibility of bariatric embolization as a new minimally-invasive image-guided therapy for morbid obesity. In this procedure specific blood vessels to the stomach are blocked in order to suppress the body's signals for feeling hungry, leading to weight loss.

Morbid obesity is currently treated with diet and exercise, medications, and with surgery. This study is designed to test the first procedure designed to help treat obesity using a minimally invasive, non-surgical, angiographic (through the blood vessel) approach.

Although there are over 40 hormones that limit food intake, there is only one hormone, ghrelin that has been shown to be to stimulate food intake. In obese patients, eating fails to suppress ghrelin levels, which is believed to prevent feeling full after a meal and to initiate overeating. Due to the potent hunger inducing effects of ghrelin, this hormone has been a target for the treatment of obesity and weight loss. More recently, ghrelin appears to have a significant role in the long-term effect of weight loss in bariatric (obesity) surgery where ghrelin levels are shown to be much lower when compared to untreated patients.

Recent data collected in both animals and in patients in small, short-term studies has demonstrated that blocking blood vessels (embolization) to particular portion of the stomach can temporarily suppress systemic levels of the appetite inducing hormone, ghrelin, leading to a prevention of short-term weight gain in animals. This procedure is an adaptation of a commonly performed procedure used to treat bleeding within the stomach. This adapted procedure has been named "bariatric embolization".

The guiding hypothesis of this study is to test that bariatric embolization results in safe and effective weight loss in morbidly obese patients. Bariatric embolization uses

devices cleared for embolization of highly vascular tumors or certain vascular malformations, but their use in the stomach to cause weight loss is investigational.

You may qualify to take part in this research study if you are morbidly obese and your physician has suggested bariatric surgery.

How many people will be in this study?

Twenty (20) people are expected to participate in this study at both sites.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Screening and pre-procedure assessment

Prior to being enrolled in the bariatric embolization trial, you will have a screening evaluation which will include the following exams, tests and procedures:

- Detailed medical history
- Physical exam
- Laboratory studies (including a glucose tolerance test, and H. Pylori serum antibody test)
- Upper GI endoscopy
- CT Angiography
- Nuclear medicine gastric motility/emptying examination

If you qualify for this trial: within 30 days of the procedure you will undergo a baseline assessment which will include:

- Medical history and physical examination including height and weight
- Hematological and biochemical investigations
 - Complete blood count (CBC)
 - Liver functions tests (LFTs)
 - Serum albumin
 - Electrolytes, urea, creatinine (EUC)
 - Serum or urine pregnancy tests
 - Fasting chemistries, including glucose and insulin , and gastric hormones (including Ghrelin)

For the two weeks prior to the procedure, you will be asked to keep a diet log, and record hunger levels, weight, and symptoms.

It is very important that you tell your doctor about all medication you are taking before receiving any research intervention(s). This includes prescription medication and over the counter medications such as cough and cold remedies, pain relievers, and antacids. Use of illegal drugs during

participation in this study is strictly forbidden and will result in you being discontinued from the study. Please ask your doctor if you have any questions about anything that you take.

Pre- and Post Procedure Medications:

You will be asked to take a daily oral proton pump inhibitor (Omeprazole 40 mg) and a daily oral cytoprotective agent (Sucralfate 4g). for two weeks prior and six weeks after the procedure in order to protect you against gastric ulcers.

Bariatric Embolization Procedure:

The bariatric embolization procedure will be performed with moderate sedation using intravenous midazolam and fentanyl .

- This procedure will take about 1 ½-3 hours.
- You will be placed on the X-ray fluoroscopy table.
- Next you will receive local anesthesia in the skin of your leg, then a different small catheter (thin tube) will be placed through the skin of your upper thigh into an artery that leads to your abdomen.
- Contrast (x-ray dye) will be injected through the catheter so your doctor can see all the blood vessels (angiogram) that bring blood to your stomach with an imaging machine (called fluoroscopy).
- Then the catheter will be directed the artery feeding the top of your stomach (fundus) and small particles will be slowly infused into the artery(ies) to block off blood flow to the fundus.
- After the particles have been delivered the catheter will be removed from your leg and your artery will be closed, and pressure will be applied to the area.

Follow-Up Visits

You will be asked to continue recording your diet, hunger levels, weight, symptoms (abdominal pain, nausea, cramping, etc) and present for follow up visits at set intervals for physical exam and serum blood tests for ghrelin levels over a 12 month period. You will be asked to present at one week and then 1, 3, 6 and 12 month for follow-up. During your 1 month visit and for each visit thereafter, your log will be recorded, a physical exam will be performed and you will be asked to fill out questionnaires. Blood testing will be performed. Endoscopic evaluation of the stomach and duodenum will be performed at 1 week, 1 month, and 6 month post-embolization. A nuclear medicine gastric motility study may be performed at 1 month and at 6 months if the baseline endoscopy is abnormal.

Incidental Findings:

A qualified person will review the CTA you are having as part of this research study just as it would be if you were having the MRIs as part of your routine medical care.

There is a possibility that while reviewing your CTA we may see an abnormality that we did not expect to see in this study. This is what is called an “incidental finding.”

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.
- The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

Future Contact

We would like your permission to contact you about other studies that you may be eligible for in the future.

Please initial your choice below:

- ☐ Yes, you may contact me in the future about other studies.
☐ No, I do not want you to contact me about other studies.

How long will you be in the study?

You will be in this study for up to 2 years.

4. What are the risks or discomforts of the study?

There are certain risks and discomforts that may be associated with this research study. Previous studies have shown the side effects to be:

Bariatric embolization procedure

Possible side effects may result from particles lodging into areas outside the targeted stomach area (called non targeted embolization), resulting in blockage of the blood vessels to the bowel, liver, gallbladder, pancreas, spleen, groin, bladder, pelvis or legs. If severe, this might require surgery to correct.

Other possible events include nausea, vomiting, inflammation of the stomach, ulceration, or bleeding from the stomach. Stomach rupture or death from this procedure is also possible. Bleeding from the area in your thigh where the catheter

goes in, allergic reaction to contrast agent or microspheres, an effect on fertility, damage (perforation) to a blood vessel which could lead to hemorrhage, a temporary contraction in a blood vessel (vasospasm), bruise in the groin area (inguinal hematoma), or injury from radiation exposure during imaging.

Blood clots in your veins (deep vein thrombosis) or lungs (pulmonary embolism) or death are unlikely but possible.

Angiography

An angiogram is a procedure in which a catheter (long narrow tube) is guided from a blood vessel in the leg (common femoral artery) into the blood vessels of the prostate artery to inject contrast (imaging dye) so your doctor can see the blood vessels.

Potential side effects include groin soreness and bruise formation, damage to or spasms (contractions) in the blood vessels as a result of guidewire and catheter manipulation that results in failure to treat the prostate, formation of a blood clot resulting in blockage of a blood vessel, infection, allergy to contrast agent or injury from radiation exposure during imaging.

Radiation Exposure:

This research study includes exposure to radiation from x-rays or gamma-rays (CT scan, gastric-emptying study, Bariatric Embolization). This radiation exposure is for research purposes only and is not part of your medical care. X-rays and gamma rays can damage the genetic material (DNA) in cells. At low doses, cells usually can repair this damage. There is some possibility that an incorrect repair may increase the risk of cancer in your lifetime. The normal lifetime risk of cancer is 25%. A radiation dose of 15 rems (a rem is a unit of radiation dose) would increase your lifetime risk to 25.6%. Additionally should you become pregnant prior to any of these three studies there would be unforeseen risks to you and/or your embryo.

The radiation exposure that you will get in this research study is approximately 6500 mrem. To put that in context, the average person in the United States gets a radiation exposure of 0.3 rem per year from natural sources, like the sun, outer space, air, food and soil. People who work with radiation (for example, x-ray technologists) are allowed a maximum exposure of 5.0 rem each year. Although these levels of radiation are thought to cause an increased risk of cancer, studies in people who work with radiation have rarely shown a measurable increase in cancer risk.

The radiation exposure described here is what you will get from this research study only. It does not include any exposure you may have received or will receive from other tests outside of this study that are a part of your medical care. Radiation risk builds up with each exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

Endoscopy:

Upper endoscopy is a very safe procedure. However it carries a very small risk of complications. Rare complications include:

Bleeding. Your risk of bleeding complications after endoscopy is increased if the procedure involves removing a piece of tissue for testing (biopsy) or treating a digestive system problem. In rare cases, such bleeding may require a blood transfusion.

Infection. Most endoscopies consist of an examination and biopsy, and risk of infection is low. The risk of infection increases when additional procedures are performed as part of your endoscopy. Most infections are minor and can be treated with antibiotics. Your doctor may give you preventive antibiotics before your procedure if you are at higher risk of infection.

Tearing of the gastrointestinal tract. A tear in your esophagus or another part of your upper digestive tract may require hospitalization, and sometimes surgery to repair it. The risk of this complication is very low — it occurs in an estimated 3 to 5 of every 10,000 diagnostic upper endoscopies.

Other risks:

You may also experience some brief and /or minor discomfort associated with the tests required.

You may experience pain or bruising associated with the needle from the blood drawing. Fainting and local infection can also occur when blood is drawn, although this is rare.

You may feel pressure when the catheter is inserted into your urethra.

While every reasonable effort will be made to ensure confidentiality of your protected and sensitive personal medical information, there is a risk this confidentiality could be compromised, although the study doctors do not expect this to occur.

You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

Future possibility of weight loss surgery will be limited after participating in this investigational study as the degree of risk of complications are not known and will need to be discussed with the surgeon.

There may be side effects and discomforts that are not yet known.

5. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in this study.

There is also a possibility that the information obtained in this study may help in the future development or improvement of treatment for patients who suffer from your condition.

6. What are your options if you do not want to be in the study?

If you decide not to join this study, other options are available. You do not have to join this study to get treatment. Other treatments include medications, surgery, and routine clinic visits.

You do not have to join this study. If you do not join, your care at will not be affected.

7. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

8. Will you be paid if you join this study?

No.

9. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.
- If you leave the study early, researchers may use or give out your health information that it already has if the information is needed for this study or any follow-up activities.

If you decide to participate in this study, it is expected that you will comply with the study requirements and periodic assessments.

If you choose to withdraw from the study or if you are asked by your personal doctor to leave the study, you must notify your study doctor immediately. If

you withdraw from the study, the study sponsor will use the information collected up to the point you decide to withdraw.

You will be informed of any new information that is learned while you are participating in this study that may affect your decision to continue your participation, and you may decide to withdraw at any time.

If you withdraw or are removed from the study, for any reason, your study doctor will ask you to have a final evaluation. This evaluation could include any of the assessments/tests previously mentioned in this document and any other procedures that the study doctor feels are medically necessary. You may be asked questions about your experience with the study treatment. You may also receive telephone calls to ask about the status of your disease.

10. Why might we take you out of the study early?

Your study doctor may also remove you from the study at any time based on the routine assessments. You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- if it is decided that another approach could improve your medical care
- You fail to follow instructions.
- if you are not coming to study visits
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, researchers may use or give out your health information that it already has if the information is needed for this study or any follow-up activities.

If you choose to withdraw from the study or if you are asked by your personal doctor to leave the study, you must notify your study doctor immediately. If you withdraw from the study, the study sponsor will use the information collected up to the point you decide to withdraw.

If you withdraw or are removed from the study, for any reason, your study doctor will ask you to have a final evaluation. This evaluation could include any of the assessments/tests previously mentioned in this document and any other procedures that the study doctor feels are medically necessary. You may be asked questions about your experience with the study treatment. You may also receive telephone calls to ask about the status of your disease.

The study sponsor may discontinue the study at any time. If the sponsor stops the study, your study doctor will arrange for appropriate treatment for you.

11. How will your privacy be protected?

Research institutions have rules to protect information about you. Federal and state laws also protect your privacy.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and other details.

Generally, only people on the research team will know your identity and that you are in the research study. However, sometimes other people at during your care may see or give out your information. These include people who review research studies, their staff, lawyers, or other staff.

People outside of this research institute may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and companies that sponsor the study.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins and Duke University and who receive your information may not be covered by this promise. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The use and disclosure of your information has no time limit. You may cancel your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phones and fax information are on page one of this consent form.

If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in the study.

12. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records or imaging from your other health care providers; however, these records will be anonymous and every reasonable effort will be made to remove information that may identify you with the record or imaging.

13. What treatment costs will be paid if you are injured in this study?

There is not a program to pay you if you are hurt or have other bad results from being in the study. However, medical care is open to you as it is to all sick or injured people.

- If you have health insurance: The costs for any treatment or hospital care you receive as the result of a study-related injury will be billed to your health insurer. Any costs that are not paid for by your health insurer will be billed to you.
- If you do not have health insurance: You will be billed for the costs of any treatment or hospital care you receive as the result of a study-related injury.

By signing this form you will not give up any rights you have to seek compensation for injury.

14. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

b. What do you do if you have questions about the study?

Call the principal investigators, Dr. Arepally and Dr. Weiss, and their team at 410-502-2835. If you wish, you may contact the principal

investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?

If you think you are injured or ill because of this study, call the principal investigators, Dr. Arepally and Dr. Weiss, and their team at 410-502-2835 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call Dr. Weiss's team at 410-502-2835 during regular office hours and at 410-283-2835 after hours and on weekends. After the tone, enter the phone number where you can be called, press the # key, and hang up.

d. What happens to Data, Tissue, Blood and Specimens that are collected in the study?

Scientists work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to both this study and to future research.

If you join this study:

- You will not own the data, or the tissue, blood, or other specimens given by you to the investigators for this research.
- Researchers of this research may study your data and the tissue, blood or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, researchers may use them for future research only with your consent or IRB approval.
- If data, tissue, blood or other specimens are in a form that we believe does not identify you, they may be shared with other academic medical centers, non-profit organizations, corporate sponsors and other commercial companies without your consent or IRB approval.
- You will not own any product or idea created by the researchers working on this study.
- You will not receive any financial benefit from the creation, use or sale of such a product or idea.

15. What does your signature on this consent form mean?

Your signature on this form means that:

- you understand the information given to you in this form
 - you accept the provisions in the form
 - you agree to join the study
- You will not give up any legal rights by signing this consent form.

**WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED
CONSENT FORM**

Signature of Participant
Date/Time

Signature of Person Obtaining Consent
Date/Time

Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)
Date/Time

**NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE
PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND,
IF APPROPRIATE A COPY OF THE CONSENT FORM MUST BE PLACED IN THE
PARTICIPANT'S MEDICAL RECORD.**